

FORM PTO-1390 (REV 10-94)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		11669 99USWO	
		U.S. APPLICATION NO. (If known, see 17 CFR 1.5)	
		unknown 09/937498	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED	
PCT/IB00/00608	31 March 2000	2 April 1999	
TITLE OF INVENTION			
STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION FORMULATION CONTAINING HUMAN GROWTH HORMONE, INJECTION CARTRIDGE THEREFOR AND STORAGE METHOD THEREFOR			
APPLICANT(S) FOR DO/EO/US			
MORITA et al			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information			
<p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371</p> <p>3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</p> <p>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ul style="list-style-type: none"> a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau) b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) </p> <p>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2))</p> <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ul style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau) b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. </p> <p>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <p>9. <input checked="" type="checkbox"/> An unsigned oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))</p> <p>10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5))</p>			
Items 11. to 16. below concern document(s) or information included:			
<p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment</p> <p>14. <input type="checkbox"/> A substitute specification</p> <p>15. <input type="checkbox"/> A change of power of attorney and/or address letter</p> <p>16. <input checked="" type="checkbox"/> Other items or information: International Publication Page, Preliminary Amendment, Abstract, Marked-up Copy, Form PCT/RO/101, Form PCT/ISA/210, Form PCT/IB/304, Form PCT/IPEA/408, 1 Sheet of Formal Drawings</p>			

U.S. APPLICATION NO (If known, see 37 CFR 1.5) unknown	INTERNATIONAL APPLICATION NO PCT/IB00/00608	ATTORNEY'S DOCKET NUMBER 11669.99USWO	
17. [X] The following fees are submitted.		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)): Search Report has been prepared by the EPO or JPO.....\$860.00			
International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)).....\$690.00			
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....\$710.00			
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(3)) paid to USPTO \$1000.00			
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)\$100.00			
ENTER APPROPRIATE BASIC FEE AMOUNT =		\$860.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	16	-20 = 0	X \$18.00 \$0.00
Independent claims	4	-3 = 1	X \$80.00 \$80.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		+ \$260.00 \$	
TOTAL OF ABOVE CALCULATIONS =		\$940.00	
Reduction by 1/2 for filing by small entity, if applicable Small entity status is claimed pursuant to 37 CFR 1.27		\$	
SUBTOTAL =		\$940.00	
Processing fee of \$130.00 for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		+ \$	
TOTAL NATIONAL FEE =		\$940.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)) The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) \$40.00 per property		+ \$	
TOTAL FEES ENCLOSED =		\$940.00	
		Amount to be: refunded \$ charged \$	
a. [X] Check(s) in the amount of <u>\$940.00</u> to cover the above fees is enclosed.			
b. [] Please charge my Deposit Account No _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed			
c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No <u>13-2725</u>			
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.			
SEND ALL CORRESPONDENCE TO Natalie D. Kadievitch MERCHANT & GOULD P.O. Box 2903 Minneapolis, MN 55402-0903		SIGNATURE: 	NAME: Natalie D. Kadievitch
REGISTRATION NUMBER 34,196			

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S/N unknown

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: MORITA et al. Serial No.: unknown
Filed: concurrent herewith Docket No.: 11669.99USWO
Title: STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION
FORMULATION CONTAINING HUMAN GROWTH HORMONE,
INJECTION CARTRIDGE THEREFOR AND STORAGE METHOD
THEREFOR

CERTIFICATE UNDER 37 CFR 1.10

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Date of Deposit. 25 September 2001

I hereby certify that this correspondence is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D C 20231

By: Omesh Singh
Name, Omesh Singh

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment.

IN THE ABSTRACT

Insert the attached Abstract page into the application as the last page thereof.

IN THE SPECIFICATION

A courtesy copy of the present specification is enclosed herewith. However, the World Intellectual Property Office (WIPO) copy should be relied upon if it is already in the U.S. Patent Office.

IN THE CLAIMS

Please amend claims 3-4 as follows:

3. (Amended) A storage container for a weakly acidic solution formulation in accordance with claim 1, wherein the elution rate of said polyvalent metal ions is 20 ppm or less.

4. (Amended) A storage container for a weakly acidic solution formulation in accordance with claim 1, wherein said polyvalent metal ions are zinc ions or aluminum ions.

REMARKS

The above preliminary amendment is made to remove multiple dependencies from claims 3 and 4.

A new abstract page is supplied to conform to that appearing on the publication page of the WIPO application, but the new Abstract is typed on a separate page as required by U.S. practice.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Marked-up Copy".

Applicants respectfully request that the preliminary amendment described herein be entered into the record prior to calculation of the filing fee and prior to examination and consideration of the above-identified application.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, Natalie D Kadievitch (Reg. No. 34,196), at (612) 336.4706.

Respectfully submitted,

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Dated: 25 September 2001

By 
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NDK:hjh

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ABSTRACT

The invention has the purpose of offering a storage container wherein flocculation and nebulation of hGH does not occur during storage of an hGH solution. A rubber stopper is formed of rubber such that when one such rubber stopper is immersed in 1 ml of a buffer solution having a pH of approximately 5.5 to 6.5 and containing a surfactant, stored while shaking for one week at a temperature of 25 °C, then the metal ion elution rate in the buffer solution is measured using atomic absorption spectrophotometry, the elution rate of polyvalent metal ions is 50 ppm or less.

09/937498

JC03 Rec'd PCT/PTO 25 SEP 2001

11669.99USWO

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3. A storage container for a weakly acidic solution formulation in accordance with [either claim 1 or 2,] claim 1, wherein the elution rate of said polyvalent metal ions is 20 ppm or less.

4. A storage container for a weakly acidic solution formulation in accordance with [any one of claims 1-3,] claim 1, wherein said polyvalent metal ions are zinc ions or aluminum ions.

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25 SEP 2001

WO 00/59562

PCT/IB00/00608

5 **Storage Container for Weakly Acidic Solution Formulation
Containing Human Growth Hormone, Injection Cartridge
Therefor and Storage Method Therefor**

5 TECHNICAL FIELD

The present invention relates to a storage container for a weakly acidic solution formulation containing human growth hormone, an injection cartridge therefor and a storage method therefor.

19 BACKGROUND ART

Human growth hormone (sometimes referred to as "hGH" below) is a single-chain polypeptide hormone composed of 191 amino acid residues. hGH can undergo decomposition by a number of routes, for example, by deamidation, flocculation, precipitation, oxidation of methionine residues and proteolysis. In order to avoid such decomposition reactions, hGH has conventionally been formulated and sold in freeze-dried form. However, recent years have seen a rising demand for the development of solution formulations for clinical reasons such as in order to improve the compliance of patients by simplifying the method of use, and various such formulations have been announced (see, e.g., PCT Application, Japanese-Language Publication No. Hei 7-809719; Japanese Patent Application, First Publication No. Hei 8-92125).

These solution formulations employ a weakly acidic buffer solution with a pH (pH 6-7) slightly less than the weakly alkaline physiological pH, pH 7-7.5, which has been conventionally employed in freeze-dried formulations. This is because slight alkalinity may cause deamidation of the hGH during storage as a solution. However, with slight acidity of pH 6-7, hGH may tend to precipitate, so that the addition of surfactants has been necessitated for long-term storage. Additionally, the present inventors have observed that even when surfactants are added, precipitation or nebulization of the hGH can occur during long-term storage of the hGH solution depending on the conditions, and the cause of this phenomenon has conventionally been completely unexplained.

On the other hand, since the rubber stoppers or rubber plungers used in injection-type solution formulations are in contact with the solution for a long time in comparison to the case where used in the container of a freeze-dried solution, problems in quality caused by the rubber stopper material can often occur. Whereas examples of problems associated with rubber stoppers include contaminants adhering to the rubber stopper, coring and sticking, a particular problem for solution formulations is the effect of elutes from the rubber stopper on the quality of the pharmaceutical

WO 00/59562

PCT/IB00/00608

5 agent. Rubber stoppers have very complicated properties both chemically and physically, and various types of elute substances from rubber stoppers are known. These are, for example, reported by L. Gramiccioni *et al.* (*Chromatographia*, 28 ('89) 545-550). However, it has yet to be examined which of the elute substances from
10 5 rubber stoppers have what type of effects on a hGH solution formulation, particularly weakly acidic solution formulations, and there have been no such reports as far as the inventors are aware.

15 Therefore, the present inventors performed diligent research in this regard, as a result of which they discovered that the formulation container, particularly the material
20 10 of the rubber stopper is an important factor in the stable storage of hGH solution formulations. That is, they discovered that metal ions dissolve from the rubber stopper during long-term storage and form conjugates with the hGH. Based on this discovery,
25 20 they found that it is necessary to use a rubber stopper in which the elution of metal ions (especially zinc ions and/or aluminum ions) under certain conditions is below a
30 25 standard amount in order to prevent degradations of the quality of the hGH solution formulation, thereby arriving at the present invention.
35 30

DISCLOSURE OF THE INVENTION

Specifically, the storage container for a weakly acidic solution formulation
30 20 containing human growth hormone according to the present invention comprises a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening; a first sealing member for sealing the first opening; and a second sealing member provided in the internal cavity of the cylindrical container, such as to be capable of moving along the internal cavity while
35 35 forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with the first sealing member for containing the weakly acidic solution formulation containing human growth hormone. The second sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not
40 40 degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.
45 45
50 50 A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the

- 5 first sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a first sealing member is immersed in 1 ml of a buffer solution containing a
- 10 5 surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.
- 15 A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the elution rate of polyvalent metal ions is 20 ppm or less
- 20 10 A storage container for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the polyvalent metal ions are zinc ions or aluminum ions.
- 25 15 An injection cartridge for a weakly acidic solution formulation containing human growth hormone according to the present invention comprises a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening; a first sealing member for sealing the first opening, having a thickness such as to be capable of being punctured by a syringe needle; and a second sealing member provided in the internal cavity of the cylindrical
- 30 20 container, such as to be capable of moving along the internal cavity while forming a continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with the first sealing member for containing the weakly acidic solution formulation containing human growth hormone. The second sealing member is composed of a type of rubber having minimal elution of metal ions.
- 35 25 Preferably, the rubber has a level of elution of metal ions which does not degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.
- 40 30 An injection cartridge for a weakly acidic solution formulation containing human growth hormone according to another mode of the present invention is such that the first sealing member is composed of a type of rubber having minimal elution of metal ions. Preferably, the rubber has a level of elution of metal ions which does not
- 45 35 degrade the human growth hormone in the formulation. More preferably, the rubber is such that after such a first sealing member is immersed in 1 ml of a buffer solution

- 5 containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a
temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in the buffer
solution as measured by atomic absorption spectrophotometry is 50 ppm or less
- 10 A method for storing a weakly acidic solution containing human growth
hormone according to the present invention comprises steps of preparing a cylindrical
container having a first opening and a second opening, and an internal cavity
connecting the first opening and second opening; providing a rubber stopper in the
internal cavity of the cylindrical container, such as to be capable of moving along the
internal cavity while forming a continuous seal in a circumferential direction with an
15 inner wall which forms this internal cavity, thereby forming a space with the first sealing
member; filling the space with the weakly acidic solution formulation containing human
growth hormone, and sealing the first opening with a cap. The rubber stopper is
composed of a type of rubber having minimal elution of metal ions. Preferably, the
rubber has a level of elution of metal ions which does not degrade the human growth
20 hormone in the formulation. More preferably, the rubber is such that after such a
rubber stopper is immersed in 1 ml of a buffer solution containing a surfactant and
having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week,
the elution rate of polyvalent metal ions in the buffer solution as measured by atomic
absorption spectrophotometry is 50 ppm or less.
- 25 20 A method for storing a weakly acidic solution containing human growth
hormone according to another mode of the present invention is such that a polyvalent
metal ion chelating agent is added to the weakly acidic solution formulation containing a
human growth hormone
- 30 The terminology such as "buffer solution containing a surfactant" used in the
35 25 present specification is defined as follows. "Buffer solution containing a surfactant"
refers to a solution containing a citric acid-type, phosphoric acid-type, glycine-type or
tris-type buffer, an isotonic agent such as sodium chloride, a surfactant such as
40 Polysorbate 80, Polysorbate 20 or Poloxamer 188, and optionally, other preservatives
and the like as needed. Polysorbate 20, Poloxamer 188 and the like are preferred as
45 30 surfactants
- "Rubber stopper or rubber plunger" refers to a rubber stopper for a syringe vial
or a plunger used in a cartridge for a convenience-type syringe formulation. That is, a
50 35 rubber stopper is a sealing plug composed of rubber used for an antiseptic seal after a
vial container is filled with hGH. A rubber plunger is a sealing plug composed of rubber
used for an antiseptic seal in an hGH solution-filled cartridge used in hGH
administration devices

5 "hGH" refers to human growth hormone which was brought into practice
almost 20 years ago as a treatment for pituitary dwarfism, of which various medical
formulations are commercially available. In the present invention, hGH includes not
only hGH proteins from the human pituitary gland (191 amino acids, molecular weight
10 5 approximately 22,000), but also to human growth hormone equivalents having
biologically specific biological activity (e.g. substitution modifications, addition
modifications, deletion modifications). Here, biological activity specific to hGH refers
mainly to overall growth accelerating activity for causing all human tissues (especially
15 bones) except for the brain to grow mainly during the developmental period, including
the effects of accelerating production of bones and cartilage by IGF-I induction,
promotion of amino acid intake to cells and protein synthesis, suppression of protein
decomposition, promotion of neutral fat metabolism, promotion of sugar metabolism
20 and promotion of electrolyte retention.

"Weakly acidic solution formulation containing hGH" refers to a solution
15 formulation having a buffer with a pH of 5.5-7, and containing hGH as an active
ingredient. The appropriate pH range for such an hGH solution formulation is 5.5-7.0,
25 and has been reported to be more advantageously 6.0 (PCT Application, Japanese-
Language Publication No. Hei 7-509719).

"Storage container" refers to a fluid storage container such as a vial or
30 cartridge for a syringe as commonly used in the field of pharmaceuticals.
According to the storage container for a weakly acidic solution formulation
containing human growth hormone, injection cartridge therefor and storage method
therefor of the present invention employing this type of structure, low levels of
35 nebulation preferably, no nebulation is observed in the storage container containing
human growth hormone, thus making it possible to offer an hGH solution formulation
which is physically and chemically stable.

BRIEF DESCRIPTION OF THE DRAWINGS

40 Fig. 1 is a side view showing a portion of a storage container according to the
present invention in cross-section.
30 Fig. 2 is a perspective view showing the state of use of the storage container
shown in Fig. 1.

BEST MODE FOR CARRYING OUT THE INVENTION

35 Herebelow, a mode for carrying out the present invention shall be described
with reference to the drawings. Fig. 1 shows a storage container according to the
present invention. The storage container 10 has a roughly cylindrical container body
50

5 12 The container body 12 forms an internal cavity 14 this internal cavity 14 being open at the openings 16, 18 at the ends thereof. In the present embodiment, one end of the container body 12 has a smaller diameter to form a mouth portion 20. The mouth portion 20 has a thin rubber cap 22 and a metallic cap 24 covering this rubber cap 22.

10 5 As shown in the drawings, these caps 22 and 24 are attached by pressing the cylindrical portion of the metallic cap 24 and the end portion of the tubular portion toward the mouth portion 20 and deforming it. The metallic cap 24 has an opening 26 opposing the opening 16 on roughly the central axis of the container body, such that by passing a needle into this opening 26 and through the rubber cap 22, it is possible to withdraw fluid from the inside.

15 In the internal cavity 14 of the container body 12, a roughly cylindrical rubber stopper 28 or rubber plunger is inserted from the opening 18 on the other side. The rubber stopper 28 has a slightly larger outer diameter than the inner diameter of the internal cavity 14 of the container body when in a state of withdrawal from the container body 12. Consequently, when the rubber stopper 28 is in a state of insertion into the internal cavity 14 of the container body 14, a continuous seal is formed between the inner wall 30 forming this internal cavity 14 and the outer circumferential surface of the rubber stopper 28, as a result of which an enclosed chamber 32 is formed between the rubber cap 26 and the rubber stopper 28, and a liquid, i.e. human growth hormone solution (weakly acidic solution formulation containing human growth hormone) 34 can be accommodated in this chamber 32.

20 When sealing human growth hormone solution 34 into the container body 12, the rubber stopper 28 is inserted from the opening 18 with the caps 26 and 28 unattached to the opening 16. Next, human growth hormone solution 34 is injected into the container body 12 from the opening 16. Finally, this opening 16 is covered with the rubber cap 22 and metallic cap 24, and the edge of the tubular portion of the metallic cap 24 is deformed towards the mouth portion 20 to close the seal. Alternatively, the opening 16 is covered with the rubber cap 22 and the metallic cap 24, and the edge of the tubular portion of the metallic cap 24 is deformed towards the mouth portion 20 to close the seal. Next, the human growth hormone solution 34 is injected into the container body 12 through the opening 18. Finally, the rubber stopper 28 is inserted from the opening 18 while compressing to deform.

25 45 The human growth hormone solution 34 contained in the storage container 12 having this type of structure is, for example, injected into a patient using the syringe device (administration device) 40 of Fig. 2 offered under the trade name "Pen 100S" from Disetronic. This syringe device 40 is composed of a holder 42 for accommodating

5 the storage container 10 and an actuator 44 coupled to the rear end of this holder 42.
Upon use, the storage container 10 is inserted into the holder 42 and the actuator is
10 fitted to the rear end of this holder 42. Additionally, a cap 46 is attached to the front end
 of the holder 42. This cap 46 is provided with a needle 48 on an end surface, the two
15 tips of this needle 48 protruding respectively from the inside end surface and outside
 end surface, the end of the needle 48 protruding from the inner end surface puncturing
 the rubber cap 22. In this state, the actuator 44 is operated, and the rubber stopper 28
 of the storage container 12 is pressed. As a result, the human growth hormone solution
 34 inside the storage container is delivered through the needle 48.

10 Herebelow, the rubber stopper of the storage container 12 shall be explained
 in detail. There are no restrictions as to the material of the rubber stopper as long as it
20 is a material capable of being used in rubber stoppers for medical purposes. Butyl
 rubber, butyl chloride rubber and butadiene rubber are known as basic elastomers, and
 any of these may be used. Additionally, while the rubber stopper (or plunger) is used in
25 combination with a vial and injection cartridge, their material and shape are not
 particularly restricted. Aside from glass which is commonly used, it is also possible to
 use, for example, synthetic resins such as polypropylene.

 A rubber stopper suitable for the solution storage container of the present
 invention is most preferably selected by the following experiments.

- 30 (1) A buffer solution (pH 6) containing a surfactant is prepared, and 1 ml is put
 into a glass vial. The above-mentioned solution may optionally include isotonicities,
 stabilizers, preservatives, anti-oxidants, solubilizers and excipients as appropriate. The
 test conditions may be changed according to the composition, storage conditions and
 method of use of the hGH solution formulation which is to be used, but in view of the
35 purpose of strictly evaluating the amount of elutes from the rubber stopper, it is
 undesirable to add agents such as chelating agents which may have an effect on the
 metal ions.
40 (2) A single rubber stopper (approximately 1 g) is immersed in the above-
 described vial, and stored while shaking at 25 °C for one week.
45 (3) The amount of metal ions which have dissolved into the buffer solution is
 measured by atomic absorption spectrophotometry.
 (4) Rubber stoppers having an elution rate of 50 ppm or less of polyvalent metal
 ions, particularly zinc and/or aluminum are selected. Preferably, those with an elution
 rate of zinc and/or aluminum ions of 20 ppm or less per rubber stopper under the
 above-given conditions are chosen.
50 (5) If the rubber stopper material fails to reach the above standards, it can be

5 modified or treated to provide it with properties suitable for the storage container of the present invention by means of surface treatment or the like. For example, by coating the rubber stopper with a fluorine resin laminate, plastic, bulk silicon or other
10 macromolecules by means of commonly known methods, it is possible to prevent the rubber stopper from directly contacting the hGH solution, thereby suppressing the elution of metal ions from the rubber stopper. Rubber stoppers coated by means of such conventional methods should be evaluated by means of the test described in paragraphs (1)-(4), and selected under similar criteria for employment in the container
15 of the present invention.

10 Unlike a rubber stopper for a vial, a plunger must use a material which is harder (there are usually more additives to the rubber) than that of a simple vial stopper due to the functional property of moving inside the cartridge during use and deciding the dosage delivered. While coatings by bulk silicon or the like which may be scraped off due to friction are not generally held to be preferable for surface treatment, it is
20 15 possible to have a coating with only a small amount of silicon in order to reduce the friction. Therefore, the plunger which is suitable for carrying out the present invention must clear standards which are more stringent than those of a normal rubber stopper for vials. Specifically, the tests described in paragraphs (1)-(3) should be performed, and those with a zinc and/or aluminum ion concentration of 20 ppm or less should be
25 20 used.

30 Herebelow, experiments performed on the rubber stoppers of the storage container shall be explained.

35 1) Method of Analysis

25 (i) Metal Ion Content

40 The quantitative analysis of metal ions in the solution was performed using atomic absorption spectrophotometry according to conventional methods.

45 (ii) hGH Content, Polymer Content

30 Size-exclusion chromatography was performed using a TSK G2000SWXL with 200 mM sodium phosphate (pH 6.8)/0.1% SDS/0.04% Polysorbate 20 as the mobile phase. The flow rate was 0.7 mL/min, and measured at 214 nm.

35 (ii) Deamidate Content

45 Anion exchange chromatography ((HPIEC) was performed using a TSK DEAE 3SW column (0.75 mm x 7.5 cm) at 40 °C with a flow rate of 1.0 mL/min. This column was equilibrated with a 25 mM bis-tris buffer (pH 5.8). Elution was performed using a 40 min gradient of 25 mM bis-tris buffer/0.5 M sodium chloride. Measurements were 50 performed at 280 nm.

- 5 2) **Experimental Method**
- (i) **Experiment 1 Effects of Metal Ions on hGH**
- 10 1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. A solution in which was dissolved zinc acetate, aluminum chloride, calcium chloride and magnesium chloride was antiseptically added to the above-described sample so as to make the metal ion concentration a standard concentration, and the changes in the solubility state were observed.
- 15 (ii) **Experiment 2 Elution of Metal Ions from Rubber Stopper**
- 20 1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. Each rubber stopper (rubber stopper B1 of Company B and rubber stoppers A1, A2, A3 and A4 of Company A) was immersed in the above-described sample, which was then stored at room temperature while shaking for a week. Thereafter, the metal ion concentration in the solution was measured.
- 25 (iii) **Experiment 3 Effects of Rubber Stopper on hGH**
- 30 1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. A rubber stopper (rubber stopper B1 of Company B) with a high metal ion elution rate was immersed in the above-described sample, and 200 ppm of 2-sodium ethylene diamine 4-acetate was added. The change in the solubilization state was observed after letting stand at room temperature for 1 week.
- 35 (iv) **Experiment 4 Effects of Various Rubber Stoppers on hGH**
- 40 1 mL of a solution formed of 1 mL of a 10 mM citric acid buffer solution (pH 6.0) with 5.0 mg of hGH, 8.77 mg of sodium chloride, 2.5 mg of phenol and 2.0 mg of Polysorbate 20 was antiseptically filled into a glass bottle. Each type of rubber stopper was immersed in the hGH solution. The pH change, content change, deamidate
- 45 3) **Experiment Results**
- (i) **Experiment 1 Effects of Metal Ions on hGH**
- 50 With regard to zinc ions and aluminum ions, nebulation was observed in samples wherein 100 ppm and 50 ppm were respectively added. On the other hand, there was no nebulation in the samples into which magnesium ions and calcium ions

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were added (Table 1).

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Metal Ion	Conc Added	0 ppm	20 ppm	50 ppm	100 ppm
Zn ²⁺	Property pH	clear 6.06	clear	clear 6.00	nebulation 5.97
Al ³⁺	Property pH	clear 6.03	clear	nebulation 5.82	nebulation 5.58
Mg ²⁺	Property pH	clear 6.08	clear	clear	clear
Ca ²⁺	Property pH	clear 6.05	clear	clear	clear

(ii) Experiment 2 Elution of Metal Ions from Rubber Stopper

5 With the rubber stopper B1 of Company B, the rate of elution of aluminum ions
 was considerably higher than in other rubber stoppers (Table 2).

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Table 2

Rubber Stopper	Zn ²⁺	Al ³⁺	Mg ²⁺	Ca ²⁺
B1	82.7	2.5	0.2	0.0
A1	0.4	0.2	0.4	0.0
A2*	0.3	0.0	0.1	0.0
A3*	17.3	1.5	0.4	0.0
A4*	3.9	1.1	0.1	0.0

Note. elution units. ppm/unit

rubber stoppers weights approximately 850 mg/unit

10 *rubber stoppers weigh approximately 240 mg/unit

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(iii) Experiment 3 Effects of Rubber Stoppers on hGH

The samples in which the rubber stopper B1 of company B were immersed
 were observed to have nebulation during storage. However, the sample in which a
 15 rubber stopper B1 of Company B was immersed after adding the chelating agent 2-
 sodium ethylene diamine 4-acetate was not observed to have nebulation (Table 3)

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Table 3

	No Rubber Stopper	Rubber Stopper Present*
EDTA 0 ppm	clear	nebulation
EDTA 200 ppm	clear	clear

* rubber stopper B1 of Company B

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After one week of stationary storage at room temperature

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5 (iv) Experiment 4 Effects of Various Rubber Stoppers on hGH

Nebulation was observed during storage of a sample in which the rubber stopper B1 of Company B was immersed, and a drop in content was confirmed (25 °C for 1 month). Additionally, in the samples in which the rubber stopper B1 of Company B was immersed, the pH of the solution rose and there was considerable generation of deamidates and polymer content.

10

Table 4

Rubber Stopper	Storage Conditions	pH	Solubility State	hGH Content ¹⁾	Deamidate Content ²⁾	Polymer Content
B1	5 °C for 1M	6.72	clear	100%	2.8%	0.8%
	25 °C for 1M	7.75	nebulation	81%	20.5%	10.4%
A3	5 °C for 1M	6.17	clear	99%	2.8%	0.3%
	25 °C for 1M	6.30	clear	102%	10.7%	1.0%
A4	5 °C for 1M	6.20	clear	99%	3.0%	0.3%
	25 °C for 1M	6.41	clear	101%	11.7%	0.6%
A1	5 °C for 1M	6.15	clear	100%	3.0%	0.2%
	25 °C for 1M	6.21	clear	100%	10.7%	0.5%
None	5 °C for 1M	6.08	clear	100%	3.2%	0.4%

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1) The hGH content was calculated with the sample content after storage at 5 °C for 1M without a stopper as 100%.

2) The deamidate content includes cyclic imides

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CLAIMS

1. A storage container for a weakly acidic solution formulation containing human growth hormone, comprising:

10 5 a cylindrical container having a first opening and a second opening, and an internal cavity connecting the first opening and second opening;
a first sealing member for sealing said first opening; and
a second sealing member provided in the internal cavity of said cylindrical container, such as to be capable of moving along said internal cavity while forming a
15 10 continuous seal in a circumferential direction with an inner wall which forms this internal cavity, thereby forming an enclosed space with said first sealing member for containing the weakly acidic solution formulation containing human growth hormone;

20 20 said storage container for a weakly acidic solution formulation containing human growth hormone being characterized in that:

25 15 said second sealing member is composed of a type of rubber such that after such a second sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

30 20 2. A storage container for a weakly acidic solution formulation in accordance with claim 1, wherein said first sealing member is composed of a type of rubber such that after such a first sealing member is immersed in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or less.

35 25 3. A storage container for a weakly acidic solution formulation in accordance with either claim 1 or 2, wherein the elution rate of said polyvalent metal ions is 20 ppm or less.

40 30 4. A storage container for a weakly acidic solution formulation in accordance with any one of claims 1-3, wherein said polyvalent metal ions are zinc ions or aluminum ions

45 35 5. An injection cartridge for a weakly acidic solution formulation containing

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- 5 human growth hormone, comprising:
10 a cylindrical container having a first opening and a second opening, and an
internal cavity connecting the first opening and second opening,
15 a first sealing member for sealing said first opening, having a thickness such
as to be capable of being punctured by a syringe needle; and
20 a second sealing member provided in the internal cavity of said cylindrical
container, such as to be capable of moving along said internal cavity while forming a
continuous seal in a circumferential direction with an inner wall which forms this internal
cavity, thereby forming an enclosed space with said first sealing member for containing
25 the weakly acidic solution formulation containing human growth hormone;
30 said injection cartridge for a weakly acidic solution formulation containing
human growth hormone being characterized in that:
35 said second sealing member is composed of a type of rubber such that after
such a second sealing member is immersed in 1 ml of a buffer solution containing a
40 surfactant and having a pH of 5.5-6.5 and stored while shaking at a temperature of 25
°C for 1 week, the elution rate of polyvalent metal ions in said buffer solution as
45 measured by atomic absorption spectrophotometry is 50 ppm or less.
- 50 6 An injection cartridge for a weakly acidic solution formulation containing
55 human growth hormone in accordance with claim 5, wherein said first sealing member
is composed of a type of rubber such that after such a first sealing member is immersed
in 1 ml of a buffer solution containing a surfactant and having a pH of 5.5-6.5 and
60 stored while shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent
metal ions in said buffer solution as measured by atomic absorption spectrophotometry
65 is 50 ppm or less.
- 7 7 A method for storing a weakly acidic solution containing human growth
hormone, comprising steps of:
80 preparing a cylindrical container having a first opening and a second opening,
85 and an internal cavity connecting the first opening and second opening,
90 providing a rubber stopper in the internal cavity of said cylindrical container,
such as to be capable of moving along said internal cavity while forming a continuous
95 seal in a circumferential direction with an inner wall which forms this internal cavity,
thereby forming a space with said first sealing member;
100 filling said space with the weakly acidic solution formulation containing human
growth hormone; and

- 5 sealing said first opening with a cap;
10 said method for storing a weakly acidic solution containing human growth
hormone being characterized in that said rubber stopper is composed of a type of
rubber such that after such a rubber stopper is immersed in 1 ml of a buffer solution
15 5 containing a surfactant and having a pH of 5.5-6.5 and stored while shaking at a
temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in said buffer
solution as measured by atomic absorption spectrophotometry is 50 ppm or less.
- 20 8. A method for storing a weakly acidic solution containing human growth
10 hormone in accordance with claim 7, comprising a step of adding a polyvalent metal ion
chelating agent to the weakly acidic solution containing human growth hormone.
- 25 9. A sealing member for a storage container for a weakly acidic solution
formulation, the sealing member comprising
15 15 a type of rubber such that after the sealing member is immersed in 1 ml of a
buffer solution containing a surfactant and having a pH of 5.5-6.5 and stored while
shaking at a temperature of 25 °C for 1 week, the elution rate of polyvalent metal ions in
said buffer solution as measured by atomic absorption spectrophotometry is 50 ppm or
less.
- 30 10. The sealing member of claim 9 wherein the elution rate of said polyvalent
metal ions is 20 ppm or less
- 35 11. The sealing member of claim 9 wherein said polyvalent metal ions are zinc
25 ions or aluminum ions.
- 40 12. A process for determining whether a sealing member is suitable for use in a
storage container for a weakly acidic solution formulation containing human growth
hormone, the process comprising the steps of:
45 30 (a) immersing the sealing member in 1 ml of a buffer solution containing
a surfactant and having a pH of 5.5-6.5;
45 (b) storing the immersed sealing member at a temperature of 25 °C for 1
week;
50 35 (c) simultaneously with step (b) shaking the immersed sealing member
at a temperature of 25 °C for 1 week; and
55 (d) measuring the elution rate of polyvalent metal ions in said buffer

5 solution.

13. The process of claim 12 wherein step (d) is performed by atomic absorption spectrophotometry.

10 5 14. The process of claim 12 further comprising a step (e) of determining that the sealing member is suitable if the elution rate measured in step (d) is 50 ppm or less.

15 15 10 The process of claim 12 further comprising a step (e) of determining that the sealing member is suitable if the elution rate measured in step (d) is 20 ppm or less

20 16. The process of claim 12 further comprising a step (e) of adding a polyvalent metal ion chelating agent to the weakly acidic solution containing human growth hormone.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION FORMULATION CONTAINING HUMAN GROWTH HORMONE, INJECTION CARTRIDGE THEREFOR AND STORAGE METHOD THEREFOR			
(57) Abstract			
<p>The invention has the purpose of offering a storage container wherein flocculation and nebulization of hGH does not occur during storage of an hGH solution. A rubber stopper is formed of rubber such that when one such rubber stopper is immersed in 1ml of a buffer solution having a pH of approximately 5.5 to 6.5 and containing a surfactant, stored while shaking for one week at a temperature of 25 °C, then the metal ion elution rate in the buffer solution is measured using atomic absorption spectrophotometry, the elution rate of polyvalent metal ions is 50 ppm or less.</p>			

Inventor MORITA et al
Docket No. 11669 99USWO
Title STORAGE CONTAINER FOR WEAKLY ACIDIC SOLUTION FORMULATION
CONTAINING HUMAN GROWTH HORMONE, INJECTION CARTRIDGE THEREFOR
AND STORAGE METHOD THEREFOR
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Sheet 1 of 1

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1/1

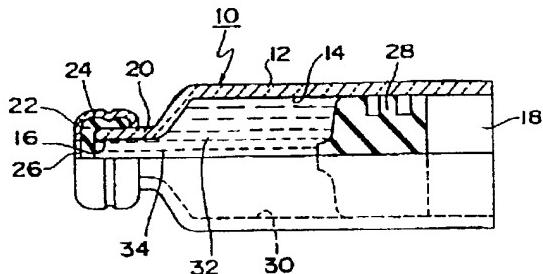


FIG. 1

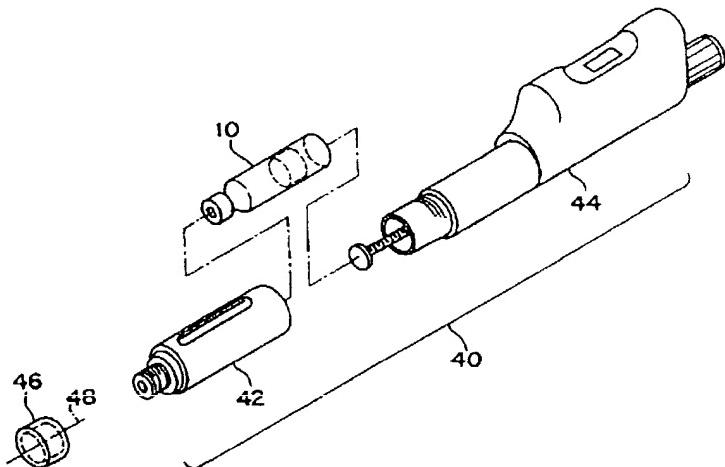


FIG. 2

Attorney Docket No. 11669.99USWO

MERCHANT & GOULD P.C.

United States Patent Application

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As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

The specification of which

- a. is attached hereto
b. was filed on 25 September 2001 as application serial no. _____ and was amended on _____ (if applicable) (in the case of a PCT-filed application) described and claimed in international no. PCT/IB00/00608 filed 31 March 2000 and as amended on (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

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COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)
Japan	11/96443	2 April 1999	

ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)

COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)

I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

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I acknowledge the duty to disclose information that is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (reprinted below):

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(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

- (1) prior art cited in search reports of a foreign patent office in a counterpart application, and
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(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

- (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
 - (2) It refutes, or is inconsistent with, a position the applicant takes in:
 - (i) Opposing an argument of unpatentability relied on by the Office, or
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A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

- (c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:
 - (1) Each inventor named in the application;
 - (2) Each attorney or agent who prepares or prosecutes the application; and
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- (e) In any continuation-in-part application, the duty under this section includes the duty to disclose to the Office all information known to the person to be material to patentability, as defined in paragraph (b) of this section, which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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